REMARKS

Claims 1-15 are pending after entry of this paper. Claims 1-5 and 14-14 have been rejected. Claims 6-9 have been objected to. Claims 10, 11, and 15 have been withdrawn from further consideration. Applicants reserve the right to pursue withdrawn claims in a divisional or continuing application.

Claims 1-4, 6-9, and 12-13 have been amended. Specifically, claims 1-4 have been amended to add the term "isolated" to explicitly indicate the hand of man. Claims 1-4 have been further amended to replace "one or a few amino acids" with the phrase "one to five amino acids." Support may be found throughout the instant specification, for example, at paragraph [0014] of the specification as filed. Finally, claims 1-3 have been amended to replace "60% or more homology" with "80% or more homology." Support may be found throughout the instant specification, for example, at paragraph [0016] of the specification as filed.

Claim 3 has been amended to define the stringent condition by incorporating the wherein clause "wherein the stringent condition comprises hybridizing at 65°C in the presence of 0.7 to 1.0 M NaCl, and washing with a 0.1 to 2-fold SSC solution (one-fold concentration SSC solution is composed of 150mM sodium chloride and 15 mM sodium citrate) under a condition of 65°C." Support may be found throughout the instant specification, for example, at paragraph [0017] of the specification as filed.

Claims 6-9 have been amended to present the claims in proper dependant form, wherein one of the reference claims was incorporated into claims 6-9.

Claims 12 and 13 have been amended to the step of estimating the test substance. Support may be found throughout the instant specification, for example, at paragraph [0034] of the specification as filed.

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Objections made to the Specification

The abstract is objected to because it recites the amino acid sequence of SEQ ID NO:2 without providing the sequence identifier "SEQ ID NO:2." (Office Action; pg. 2.) Per Examiner's request, an appropriate correction to the abstract is submitted herewith.

Furthermore, the Examiner points out that the specification at page 11, lines 9-10 erroneously refers to the "N-terminal" amino acids as the "C-terminal." (Office Action; pg. 2.) Per Examiner's suggestion, an appropriate correction to the specification is submitted herewith.

Reconsideration and withdrawal of the objections to the specification and abstract are respectfully requested.

Response to Objections made to the Claims

Claims 6-9 are objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. (Office Action; pg. 3.)

Applicants respectfully submit that claims 6-9 have been amended to comply with 37 CFR § 1.75(c). Specifically, the claims have been amended to incorporate the subject matter of one of the claims from which multiple dependency issue arisen.

Reconsideration and withdrawal of the objection to the claims 6-9 are respectfully requested.

Response to Rejections under 35 U.S.C. §101

Claims 1-4 stand rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. Specifically, the claims are directed to a peptide or a DNA that allegedly does not explicitly indicate the hand of man. (Office Action; pg. 3.). The Examiner suggests the insertion of "isolated or purified" in connection with the peptide or DNA recited in claims 1-4.

In order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 1-4 by inserting the term "isolated" in connection with the claimed DNA or a peptide. Reconsideration and withdrawal of the rejection under 35 U.S.C. §101 are respectfully requested.

Response to Rejections under 35 U.S.C. §112, first paragraph

Claims 1-5 and 12-14 stand rejected under 35 U.S.C. §112, first paragraph for lack of written description. Specifically, the Examiner contends that the instant specification does sufficiently describe a genus of variants for the amino acids within the claimed sequences. While the Examiner acknowledges that the application provides four functional variants, i.e., 1-24, 1-20, 5-24, and 2-13, the Examiner still maintains that because the specification provides no structure-activity correlation for the variants, a skilled artisan cannot predict which variant or fragment is functional. (Office Action, pg. 5.) Therefore, the Examiner concludes that "a skilled artisan would not recognize [that] applicants were in possession of the claimed invention." (Office Action; pg. 6.) Applicants respectfully disagree.

As an initial matter, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 1-4, thereby limiting the claimed amino acid sequence of SEQ ID No: 2 to an amino acid sequence that has a cardioinhibitory activity or hypotensive activity; an amino acid sequence where one to five amino acids are deleted, substituted or added, and an amino acid sequence having 80% or more homology to SEQ ID NO: 2.

Applicants respectfully assert that contrary to the Examiner, the specification as filed provide sufficient detail to apprise a skilled artisan that the applicants had the possession of the claimed invention.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice . . . , or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (MPEP § 2163).

The Examiner's attention is respectfully directed to the application as filed at paragraphs 13 and 14, which described that the claimed polypeptides are defined by their shared structural and functional features. Specifically, the sequence homology to a reference amino acid sequence (SEQ ID NO.: 2; 24 aa) is a structural property of the polypeptide, and a shared cardioinhibitory or hypotensive activity is a functional property of the polypeptide.

The specification provides five (4) working variants that span the entire scope of the claimed polypeptide genus. The original claimed sequence has 24 amino acids (1-24). Applicants identified that this sequence may be modified while preserving its desired functionality. For instance, applicants were able to delete four C-terminal residues (1-20), four

N-terminal residues (5-24), and one N-terminal and eleven C-terminal residues (2-13), yet maintain its cardioinhibitory or hypotensive activity (albeit 2-13 had reduced activity). Applicants also were able to identify the claimed sequence in other species such as rats. The amino acid sequence is represented by SEQ ID NO.: 6, with one modification at position 12 (K→ E).

The specification further provides functional assays for identifying the polypeptides with such structural characteristics. For example, the homologous peptide may be synthesized by various methodologies well known to the ordinarily skilled artisan, *e.g.*, see para. [0024] of the specification as filed. The obtained peptide that has at least 80% homology and/or no more than 5 additions, substitutions, or modifications, may be screened for the cardioinhibitory or hypotensive activity by administering the peptide to a non-human test animal via a catheter placed in the femoral artery (*e.g.*, Example 2), and the blood pressure and heart rates measured according to the methods known in the art with the use of an electromagnetic flowmeter. This assay, among others well known in the art, thus allows one skilled in the art to identify the polypeptides based on their functional attributes, i.e., cardioinhibitory or hypotensive effect. Moreover, the peptide of interest can also be screened by using an antibody that recognizes specifically the N-terminal region of the peptide. (para. [0024]). Thus, both structural and functional features commonly shared by all members of the genus of cardioinhibitory/hypotensive endogenous bioactive peptides homologous to SEQ ID NO.: 2 have been described in detail, which clearly allow persons of ordinary skill in the art to reasonably conclude that the inventor had possession of the claimed invention. MPEP § 2163.1.

Finally, applicants respectfully assert that the Examiner's contention that four exemplary polypeptides with known activity are not sufficient as a representative for the variants

of cardioinhibitory/hypotensive peptide of SEQ ID NO.: 2 is inconsistent with the written description requirement set forth in the MPEP and case law. For instance, in *Ex parte Sun* (Appeal No. 2003 1993, Bd Pat App & Int), the Examiner rejected a claim reciting an 80% sequence identity to a reference sequence for inadequate written description. The Examiner reasoned that the rejection was proper because the specification fails to teach a single representative species that has 80% identity to the reference sequence and the requisite function. The Board reversed the written description rejection, holding that, even though the specification does not specifically teach a species with the recited percentage identity and the requisite function, the fact is not dispositive of the written description question. The Board further held that, given the description of the claimed protein, its polynucleotide coding sequence, and a functional assay in the specification, and also the knowledge that certain regions of the protein are tolerant to sequence modification, the Examiner has not provided sufficient explanation or evidence to raise and maintain the written description rejection.

In the instant matter, applicants have provided far beyond what is necessary/ sufficient to satisfy written description requirement. Specifically, applicants provided (1) a polypeptide sequence, (2) activity/function, (3) a functional assay in the specification, and (4) the fact that certain regions of the peptide are tolerant to sequence modification and deletion, *i.e.*, 1-4 and 14-24. Applicants thus contend, in light of *Ex parte Sun* holding, that the written description is satisfied and respectfully request reconsideration and withdrawal of the written description rejection under 35 U.S.C. §112, first paragraph.

In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

Response to Rejections under 35 U.S.C. §112, second paragraph

Claims 1-5 and 12-14 have been rejected under 35 U.S.C. §112, second paragraph for indefiniteness.

First, the Examiner contends that what are the metes and bounds of the terms "a few amino acids" or "a few nucleotides." (Office Action; pg. 6.) Applicants respectfully disagree. However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 1-4 by replacing the term "a few amino acids" with the term "five amino acids," which readily defines the metes and bounds of the term. Support may be found throughout the instant specification, for example, at paragraph [0014] of the specification as filed.

Second, the Examiner contends that because claims 1 and 2 contain two periods, it is not clear whether or not the claim ends after the first period. (Office Action; pg. 6.) Applicants respectfully submit that appropriate corrections have been made to delete the erroneously placed first period in claims 1 and 2.

Third, the Examiner contends that the limitation "under a stringent condition" in claim 3 is allegedly not defined. (Office Action; pg. 6.) Applicants respectfully disagree. However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claim 3 to define the stringent condition by incorporating the wherein clause

> wherein the stringent condition comprises hybridizing at 65°C in the presence of 0.7 to 1.0 M NaCl, and washing with a 0.1 to 2-fold SSC solution (one-fold concentration SSC solution is composed of 150mM sodium chloride and 15 mM sodium citrate) under a condition of 65°C.

Support may be found throughout the instant specification, for example, at paragraph [0017] of the specification as filed.

Fourth, the Examiner contends that claim 12 is indefinite for using the term "32 hypotensive factor" because allegedly it is not clear what the term means. (Office Action; pg. 7.) Applicants respectfully submit that appropriate correction has been made to delete the term "32."

Fifth and final, the Examiner contends that claims 12-13 are indefinite as to how to determine the test substance is a cardioinhibitory factor or hypotensive factor, or an inhibitor of cardioinhibitory activity or an inhibitor of hypotensive activity by measuring the level of cardioinhibitory activity or hypotensive activity because it is not clear what substances are included in the control and in the testing sample for comparison. (Office Action; pg. 6.) Applicants respectfully disagree. However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 12 and 13 to clarify the steps of (1) administering, (2) measuring, and (3) estimating. Support may be found throughout the instant specification, for example, at paragraph [0034] of the specification as filed.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph to claims 1-5 and 12-14 are respectfully requested.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claim(s) 1-4 from which all of the dependent claims 5-9 and 12-14 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application. Favorable action by the Examiner is earnestly solicited. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-4827**, Order No. 1004331.037US.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-4827**, Order No. 1004331.037US.

Respectfully submitted,
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Dated: September 8, 2009

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